REMARKS/ARGUMENTS

The Present Invention

The present invention is directed to a composition comprising a dual specificity T lymphocyte comprising a recombinant chimeric receptor or recombinant T cell receptor, which is reactive with a tumor antigen, and an endogenous T cell receptor reactive with a cell that is allogeneic to the T lymphocyte, and the cell that is allogeneic to the T lymphocyte. The present invention is also directed to other related compositions and a method of preparing lymphocytes having dual specificity.

The Pending Claims

Claims 1, 4, 7, 8, 10, 40, 41, 44-46, 52-61, 71-76, and 79-93 are pending.

Discussion of the Specification

The specification of the instant application has been amended in accordance with 37 CFR 1.125 (c) (and the Manual of Patent Examination Procedure (MPEP) Section 608.01 (q)) to recite the publication number of U.S. Application No. 08/547,263 in paragraph 0052 on page 17. In view of the amendment, the status of the application no longer needs to be updated.

Discussion of the Anticipation Rejections

A. Altenschmidt

According to the Office Action, Altenschmidt anticipates claims 1, 7, 40, 41, 71, 72, 79-83, 92, and 93, because the reference allegedly discloses a composition comprising T lymphocytes comprising a chimeric receptor having antigen specificity for a tumor antigen (Erb-B2 receptor) and an endogenous T cell receptor which has antigenic specificity for an allogeneic cell, wherein the allogeneic cell is either an HC11 or HC11 R2 target cell. The Office Action specifically contends that the property of having an endogenous T cell receptor reactive with an allogeneic cell is an intrinsic property of all T lymphocytes.

The rejection in view of Altenschmidt is improper, because Altenschmidt does not disclose each and every limitation of the claims. Specifically, the T lymphocytes of

Altenschmidt do not comprise an endogenous T cell receptor which has antigenic specificity for either HC11 or HC11 R2 target cells. This is evidenced by the data shown in Figure 4 of Altenschmidt. Figure 4 demonstrates that the T lymphocytes expressing the chimeric receptor are reactive to the target cells *only* when (1) the T lymphocytes are expressing the chimeric receptor reactive with Erb-B2 receptor and (2) the target cells are expressing the Erb-B2 receptor. If the T lymphocytes of Altenschmidt comprised an endogenous T cell receptor reactive to HC11 or HC11 R2 target cells, the T lymphocytes would have reacted with the target cells, by way of lysing the target cells, in a manner independent of the expression of the Erb-B2 receptor and of the chimeric receptor. That is to say that the T lymphocytes would have reacted with HC11 or HC11 R2 cells through the endogenous T cell receptor. That was not the case, however. Therefore, the Office Action's assertion that the property of having an endogenous T cell receptor reactive with an allogeneic cell is an intrinsic property of all T lymphocytes is not correct.

The Office appears to argue in the Advisory Action that the claims are not limited to a type of allogeneic cell, such that any T cell receptor allegedly satisfies the criteria of "an endogenous T cell receptor reactive with a cell that is allogeneic to the T lymphocyte." The Office further argues in the Advisory Action that it is possible for the T cells of Altenschmidt to have *another* endogenous T cell receptor, presumably one that is reactive with HC11 or HC11 R2 target cells and that is different from the endogenous T cell receptor which does not react with the target cells.

While it is true that the claims do not limit the type of cell which is allogeneic to the T lymphocyte of the claimed composition, the claims *do* require that the allogeneic cell is present as part of the claimed composition. Therefore, if the Office still alleges that Altenschmidt anticipates the claimed compositions, wherein the HC11 or HC11 R2 target cells allegedly are the allogeneic cells, then the Office must provide evidence that the T lymphocytes of Altenschmidt comprise an endogenous T cell receptor reactive with the HC11 or HC11 R2 cells. For reasons stated above, Figure 4 of Altenschmidt evidences that the T cells do not comprise an endogenous T cell receptor reactive with the HC11 or HC11 R2 target cells. As of yet, the Office has not provided any evidence otherwise. Also, the ability to react to HC11 or HC11 R2 cells is not an intrinsic property of any T cell or any T cell receptor.

Furthermore, the Office has not provided any evidence that the T lymphocytes of Altenschmidt comprise *another* endogenous T cell receptor, presumably one that is reactive with HC11 or HC11 R2 target cells and is different from the endogenous T cell receptor which does not react with the target cells. On the contrary, T lymphocytes are endowed with T cell receptors of only a single antigen specificity. Janeway et al., *Immunobiology: The Immune System in Health and Disease*, 4th ed., Elsevier Science Ltd./Garland Publishing, 1999, page 12 (copy of which is attached hereto) evidences this fact, stating:

> Instead of bearing several different receptors, each recognizing a different surface molecule of a pathogen, each naïve lymphocyte entering the bloodstream bears antigen receptors of only a single specificity.

Therefore, it is unlikely for the T lymphocytes of Altenschmidt to have two endogenous T cell receptors, one that is reactive with HC11 or HC11 R2 target cells, and one that is not reactive with these target cells.

Even if the T cells of Altenschmidt did possess such another endogenous T cell receptor, which is reactive to the target cells, which the T lymphocytes did not, the T lymphocytes would have reacted with the target cells, by way of lysing the target cells, in a manner independent of the expression of the Erb-B2 receptor and of the chimeric receptor. That is to say that the T lymphocytes would have reacted with the HC11 or HC11 R2 target cells through this other endogenous T cell receptor. That was not the case, however.

In view of the foregoing, Altenschmidt does not disclose each and every limitation of the claim. Applicants, therefore, request that the rejection be withdrawn.

B. Beecham

According to the Office Action, Beecham anticipates claims 1, 7, 40, 45, 52, 61, 71, 72, 76, 79-83, 87, and 91-93 under 102 (a), because Beecham allegedly discloses a composition comprising (1) a population of human T lymphocytes transduced with a chimeric receptor reactive with the tumor antigen CEA and (2) tumor cell cultures, which are allogeneic to the T lymphocytes.

Applicants traverse this rejection by providing a Declaration under 37 CFR 1.131 of Patrick Hwu (which Declaration is the same as the one attached to the Reply filed on November 15, 2006). As evidenced by the Declaration, the instant invention was conceived of and reduced to practice by the inventors prior to May 1, 2000, i.e., prior to the publication date of Beecham, whenever that publication date was. While the exact publication date of Beecham has not been established, since the citation refers to "May-June 2000," even assuming arguendo the publication date is May 1, 2000, the attached Declaration under 37 CFR 1.131 shows invention prior to May 1, 2000. In view of the Declaration, a 102(a) rejection in view of Beecham is moot.

According to the Advisory Action, the Office has not entered the Declaration because Applicants have not provided a showing of good and sufficient reasons why the Declaration was not earlier presented. A Request for Continued Examination is hereby submitted. The Office is respectfully requested to enter and fully consider the Declaration.

The rejection in view of Beecham is furthermore improper, because Beecham does not disclose each and every limitation of the claims. Specifically, the T lymphocytes of Beecham, which lymphocytes express the chimeric receptor reactive with the tumor antigen CEA, do not further comprise an endogenous T cell receptor which is reactive with an allogeneic cell. The Office Action claims that the property of having an endogenous T cell receptor which is reactive with an allogeneic cell is an intrinsic property of all T lymphocytes. The Office asserts that the non-specific killing of the T lymphocytes of Beecham "*might* just evidence the act of the endogenous T cell receptor reactive with a cell that is allogeneic to the T lymphocyte" (page 5 of the Office Action, emphasis added). Inherency, however may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 20 USPQ2d 1748 (Fed. Cir. 1991).

In fact, the non-specific killing exhibited by the T lymphocytes of Beecham was explained by the authors as toxicity mediated by T-LAK cells, which are able to lyse a wide spectrum of tumor targets. See page 341, 2nd complete paragraph of the left hand column. The authors do not attribute the non-specific killing of the T lymphocytes to an endogenous receptor reactive with the tumor cells not expressing the tumor antigen.

Also, as explained above in the discussion of the anticipation rejection in view of Altenschmidt, the Office Action's assertion that the property of having an endogenous T cell receptor which is reactive with an allogeneic cell is an intrinsic property of all T lymphocytes cannot be true. If it were true, then the T lymphocytes of Altenschmidt would have lysed target cells in a manner independent of the expression of the ErbB2 receptor (on the target cells) and of the chimeric receptor (on the T lymphocytes). Therefore, the endogenous T cell receptor is not an intrinsic property of all T lymphocytes.

The Office additionally argues in the Advisory Action that the claims are not limited to a type of allogeneic cell, such that any T cell receptor allegedly satisfies the criteria of "an endogenous T cell receptor reactive with a cell that is allogeneic to the T lymphocyte."

As stated above in reference to the rejection in view of Altenschmidt, the claims require that the allogeneic cell is present as part of the claimed composition. Therefore, if the Office still alleges that Beecham anticipates the claimed compositions, the Office must provide evidence that Beecham discloses a composition comprising (1) T lymphocytes which comprise (a) a chimeric T cell receptor reactive with a tumor antigen and (b) an endogenous T cell receptor reactive with a cell that is allogeneic to the T lymphocyte, and (2) the allogeneic cell. As of yet, the Office still has not provided such evidence.

In view of the foregoing, it cannot be said that Beecham discloses a composition that meets each and every limitation of the claims. The anticipation rejection in view of Beecham, therefore, cannot stand, and Applicants request that the rejection be withdrawn.

Discussion of the Obviousness Rejections

A. Beecham in view of Terheyden and Münz

According to the Office Action, claims 1, 7, 8, 40, 41, 45, 46, 52, 56, 58, 61, 71, 72, 75, 76, 79-83, 86, 87, and 90-93 are *prima facie* obvious in view of Beecham in view of Terheyden and Münz. Specifically, Beecham allegedly teaches a method comprising activating T lymphocytes and then transducing the lymphocytes with a chimeric receptor gene, which chimeric receptor is reactive to a tumor antigen. According to the Office Action, Beecham does not teach activating T lymphocytes by co-culturing with an allogeneic cell. Also, Beecham allegedly does not teach a composition comprising the T cell expressing a

chimeric receptor and allogeneic monocytes. The Office Action contends that Terheyden cures the deficiency of Beecham by establishing that it was well known in the art to co-culture monocytic antigen presenting cells (APCs) with T lymphocytes as a routine means of activating T lymphocytes. Terheyden, according to the Office Action, does not teach *allogeneic* dendritic cells. Münz allegedly cures the deficiency of Terheyden by allegedly teaching that allogeneic stimulus, as compared to autologous stimulus, is powerful in obtaining potent CTL cells.

As the Declaration of Patrick Hwu states that the instant invention was conceived of and reduced to practice prior to May 1, 2000, Beecham is not prior art to the instant application. The rejection on this basis alone is improper.

Even if Beecham were prior art to the instant application, which it is not, the rejection of the claims in view of Beecham in view of Terheyden and Münz is improper, because the criteria to establish a *prima facie* case of obviousness have not been met. Specifically, the teachings of Beecham, Terheyden, and Münz do not teach or suggest all of the claim limitations. As discussed above, Beecham does not disclose a T lymphocyte comprising *both* a chimeric receptor reactive with a tumor antigen *and* an endogenous T cell receptor reactive with a cell that is allogeneic to the T lymphocyte. The teachings of Terheyden and Münz do not cure this deficiency.

Also, the rejection in view of Beecham in view of Terheyden and Münz is improper, because there is no suggestion or motivation in these references or in the knowledge generally available to one of ordinary skill in the art to modify Beecham or to combine Beecham with Terheyden and Münz, such that the invention would have been arrived at, at the time of filing the instant application. For example, Beecham teaches activating T cells with AIMV media supplemented with IL-2 and OKT3. However, there is no teaching or suggestion in Beecham to modify this aspect of the method of producing transduced T lymphocytes. Beecham does not, for example, discuss any problems with activating T lymphocytes by using AIMV media supplemented with IL-2 and OKT3. Therefore, upon reading Beecham, one of ordinary skill in the art at the time of filing the instant application would not have been motivated to activate the T lymphocytes by co-culturing the T lymphocytes with allogeneic cells, e.g., allogeneic dendritic cells. For the same reason, one

of ordinary skill in the art upon reading Terheyden and/or Münz would not have been motivated to modify the teachings found therein or in Beecham so that the instant invention would have been arrived at.

The Office Action contends that one of ordinary skill in the art would have been motivated to modify the teachings of Beecham, because the method of activating the T lymphocytes prior to transducing the T lymphocytes taught by Beecham was not target antigen specific.

However, Beecham was not activating T lymphocytes for the purpose of creating target antigen specific T lymphocytes. Beecham activated T lymphocytes prior to transduction, because Beecham started with peripheral blood mononuclear cells, which are a mixed population of cells comprising T lymphocytes. The activation procedure of Beecham, specifically, the OKT3 treatment, allowed only the T lymphocytes of the mixed population to proliferate, so that the T lymphocytes outnumbered the other cells of the mixed population. Beecham states to this effect:

> Although cell types other than T cells may be transduced at this stage, these contaminating cells are not stimulated to replicate under the culture conditions used, whereas treatment with OKT3 induces rapid T cell proliferation. This selective T cell proliferation quickly leads to cultures that are virtually 100% T cell in origin and effectively eliminates the influence of any contaminating cells from subsequent assays.

See first complete paragraph of the left hand column on page 334. In this regard, one of ordinary skill in the art would not have been motivated to change the teachings of Beecham to be the same as the instant invention.

In view of the foregoing, the instant claims are patentable over Beecham in view of Terheyden and Münz. Applicants, therefore, request that the rejection be withdrawn.

B. Beecham in view of Terheyden, Münz, and the '755 patent

According to the Office Action, claims 4, 10, 44, 53-55, 57, 59, 60, 73, 74, 84, 85, 88, and 89 are unpatentable over Beecham in view of Terheyden, Münz, and the '755 patent.

As discussed above, in view of the attached Declaration of Patrick Hwu, Beecham is not prior art to the instant application. The rejection in view of Beecham in view of Terheyden, Münz, and the '755 patent is improper on this basis alone.

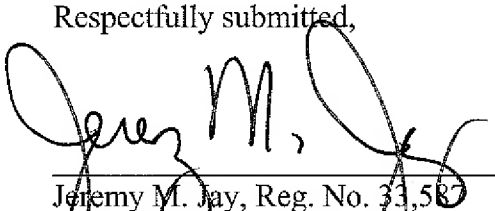
The rejection in view of Beecham in view of Terheyden, Münz, and the '755 patent is furthermore improper, because, as discussed above, Beecham does not disclose T lymphocytes comprising an endogenous T cell receptor reactive with a cell, which is allogeneic to the T lymphocytes. None of Terheyden, Münz, and the '755 patent cure this deficiency. In this regard, each and every limitation of the instant claims is not disclosed by the cited references. Therefore, the rejection cannot stand.

In view of the foregoing, the instantly pending claims are patentable over Beecham in view of Terheyden, Münz, and the '755 patent. Therefore, Applicants request the withdrawal of the rejections.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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Date: 19 Jan. 2007

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Application No. 09/803,578

Applicant: Hwu et al.

Filed: March 9, 2001

TC/AU: 1633

Examiner: Qian Janice Li

RESPONSE UNDER 37 CFR 1.116
EXPEDITED PROCEDURE

Docket No.: 218122 (Client Reference No. E-323-2000/0-US-01)

Customer No.: 45733

Commissioner for Patents
U.S. Patent and Trademark Office
Customer Service Window, Mail Stop AF
Randolph Building
401 Dulany Street
Alexandria, VA 22314

DECLARATION UNDER 37 C.F.R. § 1.131 OF PATRICK K. HWU

I, Patrick K. Hwu, do hereby declare as follows:

1. I am a co-inventor of pending claims in the above-referenced patent application, along with Steven Rosenberg and Michael Kershaw.

2. We conceived of and reduced to practice the claimed invention in the United States before May 1, 2000, as evidenced by the following:

a. attached to this Declaration is a true and accurate copy of a report prepared by another co-inventor, Michael Kershaw, who worked in my laboratory. The report, which was prepared prior to May 1, 2000, summarizes research performed involving the production and testing of dual specificity T lymphocytes, which comprised the MOVγ chimeric receptor, specific for folate binding protein (FBP), and an endogenous T cell receptor, which is reactive with allogeneic cells.

3. The date deleted from the report is prior to May 1, 2000.

4. I hereby declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 11/14/06

Patrick [redacted] Hwu, M.D.

Generation of T cells with dual specificity.

Hwu lab meeting

The limited success of adoptive immunotherapy may be due to poor persisitence and/or loss of function of adoptively transferred cells in vivo. A remedy for this may be to generate T cells with dual specificity where one specificity can be used to target tumor and the other specificity enables expansion/activation in response to a powerful immunogen.

Dual specific mouse T cells:

Aim: to raise allo-specific (H-2b anti H-2d) T cells by MLR and adoptively transfer these in vitro grown cells and see if their persistence in vivo is increased by immunization with H-2d splenocytes.

Raising T cells: 2e6 irradiated BALB/c splenocytes + 2e6 C57BL/6 splenocytes (Thy 1.1) to each 24-well (4 plates). Fed IL-2 every 2 days and split as necessary. Restim on dat 8. Day 14 16 plates ready for adoptive transfer.

In vitro function (IFN-g secretion) in response to incubation with H-2d targets:

	media	MLR cells
media	0	0
B16	0	0
24JK	0	0
CT26	0	7580
C57BL/6 spleen	0	0
BALB/c spleen	0	20230

Phenotype:

In vivo trafficking/persistence: 1e7 Thy 1.1 CTL transferred iv into Thy 1.2 C57BL/6 mice in the presence or absence of immunization with approximately 5e7 BALB/c splenocytes either iv or sq (flank and footpads). Results are expressed as amount of Thy 1.1 cells in the tissue as a percentage of total cells in the that tissue:

Thy 1.1 CTL	Immunization	Spleen		Lung		Lymph node	
		Mean	SD	Mean	SD	Mean	SD
Yes	Triple iv	0.44	0.04	0.61	0.18		
Yes	single iv	0.40	0.12	0.22	0.04		
Yes	Triple sq	4.94	1.92	1.06	0.18	11.62	1.77
Yes	single sq	1.57	0.73	0.44	0.14	4.32	4.15
Yes	none	0.69	0.12	0.24	0.10		
No	triple iv	0.00		0.00			
No	single iv	0.00		0.00			
No	triple sq	0.00		0.00		0.00	
No	single sq	0.00		0.00		0.00	
No	none	0.00		0.00		0.00	
Yes	Triple iv	33.06	10.82	10.66	7.62		
Yes	none	10.92	2.83	2.62	1.46		
No	triple iv	0.00		0.00			

Conclude that:

1. sq immunization increases % Thy 1.1 in spleen

2. triple immunization is better
3. iv immunization ineffective for spleen
4. iv immunization augments Thy 1.1 in spleens of irradiated mice
5. triple immunization may have a slight effect on numbers in lung
6. iv immunization augments numbers in lungs of irradiated mice

Having established that immunization can increase numbers of in vitro generated allo-specific CTL the next step is to make these CTL dual specific for ovarian cancer with a chimeric receptor (MOv-gamma).

First attempt at transducing MLR failed as reported last time (coculture of MLR with GP + E86 MOvg packaging cells)

Therefore next tried a different method to get rapidly dividing mouse T cells for transduction using PHA and coculture for 5 days. Pheotype:

Restimed on day 12, FACS day 17:

Cells are CD8 but have lost MOvg expression

IFN-g release on day 18:

	media	SAMEN transduced	Movg transduced
Media	3	443	220
816	1	182	66
CT26	0	808	3545
3T3	1	991	786
24JK	0	134	67
24JK-FBP	6	180	383
IGROV	0	218	1226
888 Mel	0	315	211

Cells have alloreactivity and some FBP reactivity.

Generation of dual (MOvg/Flu, MOvg/EBV) specific human T cells:

In this study M1 Flu specific or EBV-specific human T cells were generated and then transduced with chimeric MOvg. The hypothesis is that these T cells could be transferred to ovarian cancer patients and that these cells would expand/activate in response to a subsequent immunization with M1 Flu or EBV peptide.

Flu specific T cells were generated by incubation of PBMC with 1 micromolar M1. These were restimulated after 7 days with irradiated autologous M1 pulsed PBMC. 2 days later retroviral supernatant, IL-2, HEPES, polybrene were added and spinoculated. Spinoculation was repeated the next day. G418 was added 2 days later. G418 removed after 6 days. Coculture performed 2 days later.

Last meeting described 20 MOv specific clones but Flu specificity was absent. All clones except 1 were CD4 therefore it is not surprising there was no M1 reactivity.

A new culture of MK PBMC was set up with M1 and transduced following a restim as done in the first culture (which gave great expression of MOv after G418 selection) but to ensure that CD4s did not overrun this culture CD8 were enriched 2 days after transduction. Very few Cd8 cells were got and these did not thrive.

Two further M1 cultures were started with new donors. One of these cultures was transduced on days 3 and 4 of this initial stim and then examined for MOv expression before G418 but it only had about 5% expression.

These two cultures were restimed after 8 days and transduced 2 and three days later with MOvg. They have been selected in G418 for 5 days and then grown for a further 3 days now so it is time to look for expression and reactivity. Initial FACS showed about 50:50 CD4 and CD8.

If dual reactivity of bulks is demonstrated then these cells need to be cloned and/or stained with flu tetramer.

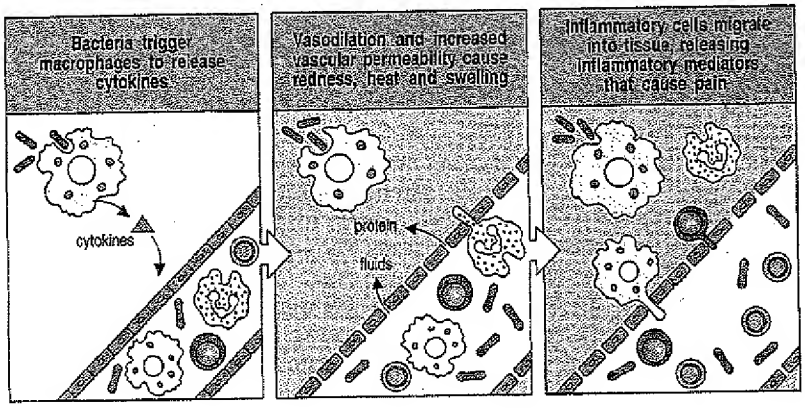

Fig. 1.12 Bacterial infection triggers an inflammatory response. Macrophages encountering bacteria in the tissues are triggered to release cytokines that increase the permeability of blood vessels, allowing fluid and proteins to pass into the tissues. The stickiness of the endothelial cells of the blood vessels is also changed, so that cells adhere to the blood vessel wall and are able to crawl through it; first neutrophils and then macrophages are shown entering the tissue from a blood vessel. The accumulation of fluid and cells at the site of infection causes the redness, swelling, heat, and pain, known collectively as inflammation. Neutrophils and macrophages are the principal inflammatory cells. Later in an immune response, activated lymphocytes may also contribute to inflammation.

blood flow and the leakage of fluid, and account for the heat, redness, and swelling. Cytokines also have important effects on the adhesive properties of the endothelium, causing circulating leukocytes to stick to the endothelial cells of the blood vessel wall and migrate between them to the site of infection, to which they are attracted by yet other cytokines. The migration of cells into the tissue and their local actions account for the pain. The main cell types seen in an inflammatory response in its initial phases are neutrophils, followed by macrophages; these are therefore known as **inflammatory cells.**

Inflammatory responses later in an infection also involve the lymphocytes of the adaptive immune response, which have meanwhile been activated by antigen that has drained from the site of infection via the afferent lymphatics. The activation of lymphocytes depends critically on interactions with phagocytic cells; bacterial constituents induce changes in the surface molecules expressed by the phagocytic cells that are crucial to the central part they play in the induction of adaptive immune responses; we shall discuss this in detail in Chapter 8.

1-6 Lymphocytes are activated by antigen to give rise to clones of antigen-specific cells that mediate adaptive immunity.

The defense systems of innate immunity are effective in combating many pathogens but they can only recognize microorganisms bearing surface molecules that are common to many pathogens and that have remained unchanged in the course of evolution. Such highly conserved molecules can be recognized by the neutrophils and macrophages of vertebrates. Not surprisingly, many bacteria have evolved a protective capsule that enables them to conceal these molecules and thereby avoid provoking phagocytic cells. Viruses carry no such unvarying molecules and are rarely recognized by phagocytic cells. Moreover, the surface molecules of pathogens evolve much faster than could any ordinary vertebrate recognition system. The recognition mechanism used by the lymphocytes of the adaptive immune response has evolved to overcome these problems.

Instead of bearing several different receptors, each recognizing a different surface molecule of a pathogen, each naive lymphocyte entering the bloodstream bears antigen receptors of only a single specificity. However, the specificity of these receptors is determined by a unique genetic mechanism that operates during the development of lymphocytes in the bone marrow